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EDITORIAL

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Managing appendicitis during the COVID-19 pandemic—What do we need to know from the evidence?

Nearly 300 years since Claudius Amyand performed the first recorded appendicectomy at St George's Hospital in London, appendicectomy has become one of the most common surgical procedures performed. Almost 10% of adults will be diagnosed with appendicitis in the USA and Europe during their lifetime,[1] with surgical treatment largely considered the treatment of choice since Fitz, Hancock and McBurney shifted the paradigm in the 19th Century.[2] At the zenith of operative management in the late 20th and early 21st centuries, 300 000 appendicectomies were performed a year in the United States of America (USA) and 25 000 in England.[3,4] Until very recently, these have largely been performed laparoscopically, with a wealth of evidence of benefits over open surgery.[5]

However, this paradigm of operative management has been challenged; whilst the incidence of appendicitis (both complicated and uncomplicated) has remained static, since 1990 1.5% fewer appendicectomies have been performed every year.[6] The evidence underpinning this shift towards non-operative treatment of appendicitis (NOTA) largely comes from eight randomised controlled trials (RCTs)[7-14] and their synthesis by systematic meta-analyses. Their conclusions have varied, but NOTA undoubtedly represents a valid treatment option for certain patients and circumstances.[15-17] Nevertheless, the vast majority of patients continue to be treated with surgery.[6]

Then in early 2020 this paradigm was thrown back into focus, viewed through an entirely different lens. Healthcare providers, in the face of capacity being or potentially being overwhelmed suddenly needed to rationalise resources and minimise transmission of COVID-19. In the United Kingdom (UK) the Royal Colleges of Surgeons advised NOTA be implemented "*Where…possible and reasonable (such as for early appendicitis),*" and that because of the unknown potential risk of viral transmission laparoscopy only be considered *"in selected individual cases where…benefit to the patient substantially exceeds the risk of potential viral transmission"*.[18] Whilst in the USA and elsewhere in Europe specialty bodies did not recommend against laparoscopic surgery,[19] the American College of Surgeons supported managing *"uncomplicated appendicitis [with] a trial of antibiotics….based on the surgeon's judgement and the patient's condition"*.[20] Other healthcare systems and providers have followed similar advice; for example, recommendations for NOTA in all but perforated appendicitis suggested on imaging in Italy and recommending against laparoscopy in the absence of dedicated protective measures.[21]

Core to these recommendations is that appendicitis comprises a spectrum of severity, with "early" or "uncomplicated" appendicitis less severe. However, these categories are more nuanced than they might at first appear; whilst most surgeons would agree complicated appendicitis includes pathology such as perforation with free faeces or pus, does this include a tiny walled-off abscess? Or an intact yet necrotic appendix? Or patients with none of the above but physiological features of sepsis ?[22] Ultimately, identifying patients for whom antibiotics will probably work and those for whom they will probably fail is key. So how to do this? Central to this is understanding the evidence base behind NOTA.

The headlines of some RCTs and meta-analyses form the basis of these recommendations: indeed, the first meta-analysis (of four RCTs) found NOTA to be, "*effective and safe as primary treatment for uncomplicated appendicitis*".[15] Since this there have been at least six meta-analyses of RCTs in adults; the author's own included six RCTs and 1724 patients, predating two subsequent RCTs,[13,14] whilst subsequent meta-analyses have included non-randomised cohorts.[23-25] These are able to help us answer some very important questions when potentially extrapolating this evidence suddenly and on a huge scale.

First, how effective is NOTA in the short-term? The author's own analysis found a failure rate (patients managed with NOTA who needed surgery during their index admission) of just 9% per protocol,[17] almost identical that that including non-randomised and retrospective studies.[23,24] So, NOTA seems to work in the short-term for most patients selected to these trials and who did not undergo treatment cross-over (both important qualifiers).

Second, how effective is NOTA in the medium to long-term? Follow-up data have largely been limited to 1 year, other than a recent 5-year update.[26] Meta-analysed rates of recurrent appendicitis rates at 1 year were 17%,[17,24] making the failure rate of NOTA approximately 25% at 1 year. This was almost identical in the APPAC trial at 1 year, but this reached 39% at 5 years.[26]

Third, how safe is NOTA? There are three broad aspects to this: the consequences of initial failure of antibiotics (ie, needing more complicated surgery later), the loss of information by not resecting the appendix and the relative complications of treatment. Meta-analyses have reported variable answers, indicative of underlying variability in how these are quantified and qualified in RCTs. In the author's analysis, whilst there was no difference overall in the risk of complicated appendicitis patients in whom antibiotics failed in the short-term were much more likely to have complicated appendicitis

(relative risk 6.2, constituting 35% of patients treated per protocol),[17] as confirmed subsequently.[23] Unsuspected tumours (mainly adenocarcinomas and neuroendocrine, importantly not evident on diagnostic computed tomography [CT] scans) were identified in 0.59% of patients undergoing surgery[17] which would not have been identified in patients undergoing NOTA. Synthesising complication data are difficult as a result of differences in how these were reported (for example, reporting any episodes of abdominal pain following surgery as a complication due to adhesions); overall, however, the author found no differences in major or minor complications.[17] This has been supported[23] but also challenged,[15,25] but is significantly affected by assessment bias of complications and their relative severity. It is similarly difficult to synthesise pain and function, but unsurprisingly RCTs have reported less pain and functional impairment following NOTA.[14,17]

Fourth, what are the implications for resource management? Almost all RCTs have stipulated patients treated with NOTA remain in hospital for at least 24-48 hours; hence, there does not yet appear to be any saving in length of admission,[17] although again some reductions have been reported when including non-randomised data[25] and there are undoubtedly savings in term of operations. The notable exception is the pilot trial of 30 patients by Talan et al, which concluded discharge from the Emergency Department was feasible within 6 hours, in conjunction with once daily intravenous antibiotics and serial review.[14]

So to summarise these RCTs: for selected patients meeting their inclusion criteria, NOTA seems to work in the short-term for 90% of patients, but fails in the medium term in a quarter (1 year) and in the long-term in nearly a half (5 years). Patients in whom NOTA fails in hospital are much more likely to have complicated appendicitis, but overall there do not seem to be any clear differences in outcome other than a probable reduction in pain for patients not undergoing surgery. There is also a small but important risk of missing an underlying malignancy in 0.5% of patients.

Of course, the key qualifier here is "for patients meeting their inclusion criteria," as these are not unselected patients with appendicitis and differences in their selection introduces bias. Generally, exclusion criteria effectively amounted to patients in whom there was radiological or clinical evidence of a perforation or abscess. Clearly, "clinical evidence" of complicated appendicitis as a criterion when selecting patients for surgery is extremely subjective. Beyond this, some trials excluded patients over the age of 50,[9] 60[26] and 70,[13] female patients[9] and patients with significant comorbidities,[14,26] patients with a faecolith[13,26] or an appendix greater than 11 mm[13] or 15 mm[11] in diameter. These caveats are reflected in the recent World Society of Emergency Surgery (WSES) Guidelines, which recommends discussing NOTA as a "*safe alternative in 'selected patients with uncomplicated appendicitis and absence of a faecolith, advising of the possibility of failure and misdiagnosing complicated appendicitis"*.[27] Specifically, the WSES advice against NOTA in pregnancy.

How these patients were diagnosed is also important. Only one study used clinical diagnosis alone[9]; one required an ultrasound scan,[12] two an ultrasound or CT[8,14] and the rest CT. This is particularly relevant to systems often relying on clinical diagnosis such as the UK and might suggest a need to image all patients in whom we are considering NOTA, to make the diagnosis and align with these inclusion criteria. There are other sources of bias meaning the overall GRADE quality of conclusions in the author's analysis was either "low" or "very low," including crossing-over within trials,[8] variable prophylactic antibiotic provision and 75% of appendicectomies being performed open.[17]

The latter is especially topical with a sometimes wholesale move away from laparoscopic surgery because of a largely theoretical and unquantified fear of viral transmission to healthcare staff through aerosols (28). Particularly in patients with negative COVID-19 test results this needs to be very carefully considered when a considerable body of evidence supports laparoscopy as the best treatment for patients with appendicitis[5] (29) and a valuable test which often identifies alternate pathology.

What all this means in practice for us and our patients of course varies with circumstance and context. What is crucial is that we fully inform patients as to these circumstances and their competing interests, framing the best evidence available with these to help patients make fully informed decisions. It is particularly important to recognise, acknowledge and discuss the uncertainty inherent in outcomes for individual patients, and the evidence for NOTA and particularly risk and benefit in the era of COVID, above all remembering our duty to individual patients first and foremost and our prima facie principles of medical ethics. Whether the COVID-19 pandemic will prove the ultimate trial of NOTA that shifts the paradigm is similarly uncertain, but the results are keenly awaited (30).

DISCLOSURE

The authors have declared no conflicts of interest for this article.

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REFERENCES

1. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet*. 2015;386:1278-1287.
2. McBurney C. Experience with early operative interference in cases of disease of the vermiform appendix. *NY Med J*. 1889;50:676-684.

3. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol*. 1990;132:910-925.
4. Al-Khyatt W, Mytton J, Tan BHL, et al. A population-based cohort study of emergency appendectomy performed in England and New York State. *World J Surg*. 2017;41:1975-1984.
5. Jaschinski T, Mosch CG, Eikermann M, Neugebauer EAM, Sauerland S. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev*. 2018 Nov 28;11:CD001546.
6. Ferris M, Quan S, Kaplan BS, et al. The global incidence of appendicitis: a systematic review of population-based studies. *Ann Surg*. 2017;266:237-241.
7. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA*. 2015;313:2340-2348.
8. Hansson J, Korner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg*. 2009;96:473-481.
9. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicenter randomized controlled trial. *World J Surg*. 2006;30:1033-1037.
10. Turhan AN, Kapan S, Kutukcu E, Yigitbas H, Hatipoglu S, Aygun E. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg [Turkish J Trauma Emerg Surg]*. 2009;15:459-462.
11. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. *Lancet*. 2011;377:1573-1579.
12. Eriksson S, Granstrom L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg*. 1995;82:166-169.
13. Park HC, Kim MJ, Lee BH. Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. *Br J Surg*. 2016;104:1785-1790.
14. Talan DA, Saltzman DJ, Mower WR, et al.; Olive View–UCLA Appendicitis Study Group. Antibiotics-first versus surgery for appendicitis: a US pilot randomized controlled trial allowing outpatient antibiotic management. *Ann Emerg Med*. 2017;70:1-11.e09.
15. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ*. 2012;244:e2156.
16. Mason RJ, Moazzez A, Sohn H, Katkhouda N. Meta-analysis of randomized trials comparing antibiotic therapy with appendectomy for acute uncomplicated (no abscess or phlegmon) appendicitis. *Surg Infect*. 2012;13:74-84.
17. Findlay JM, el Kafsi J, Hammer C, Gilmour J, Gillies RS, Maynard ND. Nonoperative management of appendicitis in adults: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Surg*. 2016;223:814-824.e2.
18. Association of Surgeons of Great Britain & Ireland, Association of Coloproctology of Great Britain & Ireland, Association of Upper Gastrointestinal Surgeons, Royal College of Surgeons of Edinburgh, Royal College of Surgeons of England, Royal College of Physicians and Surgeons of Glasgow, Royal College of Surgeons in Ireland. Updated Intercollegiate General Surgery Guidance on COVID-19. [Online] 2020. https://www.rcseng.ac.uk/coronavirus/joint-guidance-for-surgeons-v2/. Accessed May 20, 2020.
19. EAES, SAGES &.SAGES and EAES recommendations regarding surgical response to COVID-19 crisis. [Online] 2020. https://www.sages.org/recommendations-surgical-response-covid-19/. Accessed May 20, 2020.
20. American College of Surgeons.COVID-19 Guidelines for Triage of Emergency General Surgery Patients. [Online] 2020. https://www.facs.org/covid-19/clinical-guidance/elective-case/emergency-surgery. Accessed May 20, 2020.
21. Buonpane C, Goldstein S. Defining the disease: uncomplicated versus complicated appendicitis. In: Hunter C, eds. *Controversies in Pediatric Appendicitis*. Cham, Switzerland: Springer; 2019;7-11.
22. Podda M, Gerardi C, Cillara N, et al. Treatment and appendectomy for uncomplicated acute appendicitis in adults and children: a systematic review and meta-analysis. *Ann Surg*. 2019;270:1028-1040.
23. Podda M, Gerardi C, Cillara N, et al. Antibiotic treatment and appendectomy for uncomplicated acute appendicitis in adults and children: a systematic review and meta-analysis. *Surgeon*. 2017;15:303-314.
24. Yang Z, Sun F, Ai S, Wang J, Guan W, Liu S. Meta-analysis of studies comparing conservative treatment with antibiotics and appendectomy for acute appendicitis in the adult. *BMC Surg*. 2019;19:110.
25. Salminen P, Tuominen R, Paajanen H, et al. Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA*. 2018;320:1259-1265.
26. Association of Laparoscopic Surgeons of Great Britain and Ireland.Laparoscopy in The Covid-19 Environment – ALSGBI Position Statement You are here. [Online] 2020. https://www.alsgbi.org/2020/04/22/laparoscopy-in-the-covid-19-environment-alsgbi-position-statement/. Accessed May 25, 2020.
27. Boyd-Carson H, Javanmard H, Daliya P, et al.HAREM Study: Had Appendicitis and Resolved/Recurred Emergency. [Online] 2020. https://www.rcseng.ac.uk/-/media/files/rcs/standards-and-research/research/covid-research-group/updated--the-harem-study-protocol-v42.docx. Accessed May 25, 2020.